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UCLA SCHOOL OF MEDICINE
HARBOR - UCLA MEDICAL CENTER
DEPARTMENT OF RADIOLOGY
1000 CARSON STREET
TORRANCE, CALIFORNIA 90509

Dockets Management Branch
HFA-305
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

Re: Docket No. 90N-0302;FR 62(147):40996-41001, 31 July 97. Accessibility to New Drugs for Use in Military and Civilian Exigencies when Traditional Human Efficacy Studies are Not Feasible; Determination Under the Interim Rule that Informed Consent Is Not Feasible for Military Exigencies; Request for Comments.

Dear Sir/Madam:

Thank you for the opportunity to comment on this issue and FDA's Interim Rule. I am writing this letter as an individual, not on behalf of any organization. I am at present a consultant to both CBER and CDRH, and am the immediate past Chair of the Radiologic Devices Advisory Panel. I served two terms on the Radiopharmaceutical Advisory Committee (now MIDAC) at CDER, and was a consultant to that committee for several years afterwards. I am currently the Chair of one of the two IRB's of UCLA's School of Medicine, and have been involved in human research for about 27 years. I completed residencies in internal medicine and nuclear medicine; I am now practicing the latter. I also have a Ph.D. in Physical Biology with extensive experience studying physiology and biochemistry with radioactive tracers. I am presently the Southern California area individual on the Oak Ridge IND no. 4041 (Ca-DTPA) and no. 14,603 (Zn-DTPA) for emergency chelation therapy in the event of contamination with plutonium and other transuranic elements such as americium, californium, and curium.

(1) Revoking or Amending the Interim Final Rule

I oppose either revoking or amending the Interim Final Rule. I believe that the arguments of the Asst. Secretary of Defense, Health Affairs, DOD, are sufficient to retain the Interim Final

Rule language without change. The arguments of Public Citizen were not compelling. The organization and activities of the DOD are not meant to be either democratic or reliant upon informed consent. However, the goal of DOD activities in combat situations is victory, and with that end in sight, it is reasonable to expect that the condition of the troops is considered carefully by DOD leadership. Decisions pertinent to the use of investigational drugs without informed consent will most likely represent the best interests of military personnel and the nation.

(2) Evidence Needed for Safety and Effectiveness in the Face of Unethical Clinical Trials

Obviously if some of these "investigational" drugs were to be "approved", informed consent would be unnecessary, the argument would be moot, but the risks to human subjects would be unchanged. Contrary to popular opinion, FDA does not usually approve "safe" drugs. It approves drugs whose known risks are less onerous than the risks of the disease states being prevented, ameliorated, or cured. FDA's Medwatch Program was set up to identify previously unreported risks, so that the risk/benefit tradeoff may be re-estimated. A Medwatch reporting mechanism would be especially useful when evaluating drugs with no or limited human use for emergency administration, such as the Gulf War agents discussed. Surrogate end points for evaluation could be animal data, of course, and could include any small population of people who might constitute a useful group with some sort of expedited treatment IND exemption available. People in peacetime do accidentally get exposed to noxious chemicals with CNS effects. Immediate availability of an investigational drug, without requiring any institutional review before use, would be a consideration if it was pre-approved by a federally-appointed IRB with advance "buy in" from local IRB's for emergency use. A local IRB could approve use of this "class" of drugs. This would be a "situational" class, rather than a "pharmacologic" class, and could cover multiple drugs. Physicians who use these drugs would be asked to submit a report on drug safety, efficacy, usage hints, etc., once the particular crisis situation was resolved.

A similar situation exists with Ca-DTPA/Zn-DTPA. The reason I am now on the Oak Ridge IND's is that a worker in a Los Angeles area company making radioactive sources had an accidental contamination, and the drugs were unavailable in this area. After

local radiologic health personnel succeeded in bringing it in from outside and finding a nuclear medicine physician to use it, I was asked to join the IND and stock it. Each patient so treated (a very rare event) will be reported to Oak Ridge, and to my IRB. This drus combination should be approved and available to any physician, with an extensive package insert that included a case report form, updated as data permit. The holder of the NDA could be DOE, DOD, NIH, CDC, or some other federal entity if no commercial supplier wanted this responsibility.

In summary, I believe that surrogate end points in animals, and perhaps in a few human subjects if available, constitute all that is needed for such emergency drugs to be approved and released in emergency circumstances.

There is no reason why FDA should try to achieve uniformity among all drugs in the approval process. It simply inhibits drug availability in time of need for the peculiar class discussed here. There has been much appropriate pressure on FDA to make a different set of requirements for diagnostic radiopharmaceuticals, which are virtually risk-free. The FDA does not serve the public with its "one size fits all" policy. A change for drugs useful during chemical and biological warfare is a change in the right direction, and separate mechanisms should be pursued for other drug products as well.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.
Director, Nuclear Med. Outpt. Clinic
and
Professor of Radiological Sciences,
UCLA

cc: Michael A. Friedman, M.D.,
Acting Commissioner

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